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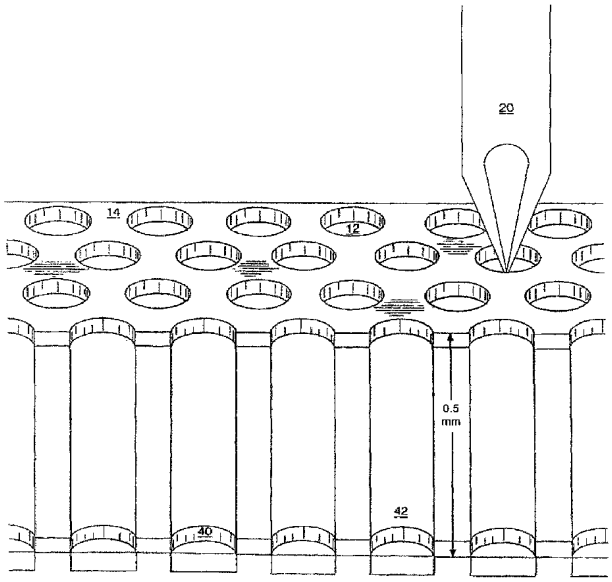
(54) Title: CAPILLARY ACTION TRANSFER PINS



(57) Abstract: A liquid dispenser for a microfluidic assay system is described. The dispenser includes at least one transfer pin for transferring a microfluidic sample of liquid to a target receptacle. A pin tip at one end of the transfer pin is structured to cooperate with an opening in the target receptacle. The pin tip uses capillary action to transfer the sample from the pin to the receptacle.

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Capillary Action Transfer Pins

Field of the Invention

The invention generally relates to techniques for assaying small volumes of liquid, and more specifically to physical transfer of a small volume into a storage medium.

Background Art

Techniques are rapidly developing for parallel performance of a large number of chemical and biological assays and synthesis operations. One approach uses a nanotiter plate having a high density platen of through-hole wells with hydrophilic interiors and openings surrounded by hydrophobic material. This is described, for example, in U.S. Patent 6,387,331 and U.S. Patent Application 20020094533, the contents of which are incorporated herein by reference. One specific commercial example of a nanotiter plate system is the Living Chip™ made by Biotrove, Inc. of Cambridge, MA. Nanotiter plate technology relies on the ability to handle very small volumes of fluid samples, typically, 100 nanoliters or less. The various considerations taken into account in handling such small liquid samples are known as microfluidics.

Transferring of large collections of fluids such as libraries of small molecule drug candidates, cells, probe molecules (*e.g.*, oligomers), and/or tissue samples stored in older style 96- or 384-well plates into more efficient high density arrays of microfluidic receptacles such as a nanotiter plate can consume one or more hours, during which time samples may evaporate, degrade or become contaminated. It is therefore advantageous to submerse the array in a bath of immiscible fluid. The fluid is ideally electrically insulating, non-conductive and nonflammable, with a relative permittivity >1. One class of fluids that serves this purpose is perfluorinated hydrocarbons, such a perfluorodecalin, perfluorooctane, perfluoropentane, longer chained perfluorocarbons or mixed populations of perfluorocarbons. Hydrocarbons or silicone fluids would also work but are flammable and tend to extract compounds from the sample.

A microfluidic volume of a liquid sample may be loaded into a target receptacle by various means. One established method for transferring a liquid sample to a surface or to another liquid uses a transfer pin loaded with the sample liquid. For example, pins or

arrays of pins are typically used to spot DNA samples onto glass slides for hybridization analysis. Pins have also been used to transfer liquids such as drug candidates between microplates or onto gels (one such gel system is being developed by Discovery Partners, San Diego, CA). Many pin types are commercially available, of various geometries and delivery volumes. V&P Scientific of San Diego, CA makes slotted, grooved, cross-hatched, and other novel-geometry pins. The Stealth Pin by ArrayIt is capable of delivering hundreds of spots in succession from one sample uptake, with delivery volumes of 0.5nL to 2.5nL. Majer Precision Engineering sells pins having tapered tips and slots such as the MicroQuil 2000.

U.S. Patent 6,149,815 describes an approach for dispensing liquid samples electrokinetically. A complex apparatus positions a capillary tube receiver reservoir and a non-conducting liquid dispenser between a ground plate and a high voltage plate, neither plate being electrically connected to a sample. An accurate volume of liquid sample is transferred from the dispenser to the receiver reservoir by precisely controlling the time that a high voltage is applied to the dispenser, the longer the voltage is applied, the greater the volume of sample transferred, and vice versa. As shown in Fig. 1 of the '815 patent, it is important to provide an insulating gap between the electrically charged dispenser and the electrically grounded receiver reservoir. Moreover, the '815 patent approach requires determining by visual observation the relationship between time, voltage, and volume of liquid transferred.

Summary of the Invention

A representative embodiment of the present invention includes a liquid dispenser for a microfluidic assay systems including systems for arraying liquid samples for storage, screening and synthesis. The dispenser includes at least one transfer pin for transferring a microfluidic volume of sample liquid to a target receptacle. A pin tip at one end of the transfer pin is structured to cooperate with an opening in the target receptacle. The pin tip creates a liquid bridge to the target receptacle to dispense sample liquid from the pin tip to the target receptacle. Dispensed sample liquid is retained in the target receptacle by means of surface tension.

In a further embodiment, the target receptacle is one of an array of through-holes wells or closed-end wells in a platen. The target receptacle may have hydrophilic walls

that attract the sample liquid. The target receptacle may have an opening surrounded by hydrophobic material. The target receptacle may be filled with a porous hydrophilic material. A transfer pin array may include multiple transfer pins for transferring multiple samples to corresponding target receptacles. Individual transfer pins in the array may be individually actuable, as would be useful for producing sample patterns or layered sample patterns. Typically the spacing of pins in the array will match a subset of a source array such as a 384 well microtiter plate as well as the spacing of the receptacle array. At least one transfer pin in the array may be independently positionable to align the at least one independently positionable pin with respect to the opening of a target receptacle. Positioning systems are typically capable of accurate movement in at least the x, y and z coordinates. Individual transfer pins in the array may be free floating or spring loaded.

In various embodiments, the dispensed sample may be from 0.2 to 100 nanoliters. The transfer pin may have a diameter greater than the opening of the target receptacle. The sample liquid may be a polar liquid such as aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solutions. An optional high voltage differential may be applied across the pin-receptacle gap to aid in the transfer. The high voltage potential, for example between 100V and 5kV, may be applied to at least one of the pin tip and the target receptacle to aid the capillary action.

In a further embodiment, a voltage control module controls when the high voltage potential is applied to and removed. The voltage control module may operate to apply the high voltage potential before or after the transfer pin is positioned at the target receptacle, and to remove the high voltage potential before or after the transfer pin is moved away from the target receptacle. The voltage control module may include a resistor network and/or a controllable switch in series with the transfer pin.

The at least one transfer pin may be able to dispense multiple samples without replenishment. The capillary action may be aided by vibrating at least one of the pin tip and the target receptacle. The pin tip may have a slotted end, for example, an X-shaped slotted end. The pin tip may have one or more structural features that increase the surface area of the sample liquid at the pin tip. These structural features may include one or more features from the group of slots, grooves, and spirals. The target receptacle may be substantially empty prior to transferring the sample liquid.

Embodiments of the present invention also include a method for use in dispensing a

microfluidic sample of a liquid. The method includes providing at least one transfer pin for transferring a microfluidic sample of liquid to a target receptacle. One end of the transfer pin may have a pin tip structured to cooperate with an opening in the target receptacle. Capillary action between the pin tip and the target receptacle is used to transfer the sample liquid from the at least one transfer pin to the target receptacle.

In such an embodiment, the target receptacle may be a through-hole well or a closed-end well in a platen array. The target receptacle also may include hydrophilic walls that attract the sample liquid and/or an opening surrounded by hydrophobic material. A high voltage potential, for example, between 100V and 5kV, may be applied to either the transfer pin or the target receptacle to aid the capillary action. The high voltage potential may be applied before or after the transfer pin is positioned at the target receptacle, and removed after the transfer pin is moved away from the target receptacle. The controlling step may use a resistor network and/or a controllable switch in series with the transfer pin.

The method may also include providing a transfer pin array including multiple transfer pins for transferring multiple samples to corresponding multiple target receptacles. Individual transfer pins in the array may be individually-actuable, either sequentially or in parallel. At least one transfer pin in the array may be independently positionable for alignment with respect to the opening of a target receptacle. Individual transfer pins in the array may be free floating or spring loaded.

In such a method, the dispensed sample may be from 0.2 to 100 nanoliters. The transfer pin may have a diameter greater than the opening of the target receptacle. The sample liquid may be a polar liquid such as aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solutions. The at least one transfer pin may be able to dispense multiple samples without replenishment.

The method may further include applying evaporation control measures to the target receptacle. This may include immersing the target receptacle in an immiscible liquid such as a perfluorinated hydrocarbon. Alternatively, or in addition, the evaporation control measures may include at least one of humidity control, fluid pressure, and receptacle cooling.

The method may also further include positioning the transfer pin in direct contact with target receptacle, or positioning the transfer pin near the target receptacle without direct contact. The method may also include sequentially transferring multiple samples to

the target receptacle to produce a layered sample pattern.

An embodiment may aid the capillary action by vibrating the transfer pin or the target receptacle. The pin tip may have a slotted end, for example, an X-shaped slotted end. The pin tip may have one or more structural features that increase the surface area of the sample liquid at the pin tip. These structural features may include one or more features from the group of slots, grooves, and spirals. In the method, the target receptacle may be substantially empty prior to transferring the sample liquid.

Another embodiment of the present invention includes a microfluidic assay system. The system includes at least one liquid sample storage device including multiple storage receptacles, a microfluidic dispenser, and a dispenser positioning module. The microfluidic dispenser has at least one transfer pin for using capillary action to transfer a microfluidic sample of liquid to a target storage receptacle, one end of the transfer pin having a pin tip structured to cooperate with an opening in the target storage receptacle. The dispenser positioning module positions the liquid dispenser to enable the transfer pin to cooperate with the target receptacle for transferring the sample liquid.

In a further such embodiment, the storage device may be a platen array of through-holes or wells. The target storage receptacle may include hydrophilic walls that attract the sample liquid and/or an opening surrounded by hydrophobic material. The liquid dispenser may also include a transfer pin array including multiple transfer pins for transferring multiple samples to corresponding multiple target storage receptacles. Transfer pins in the array may be individually actuable, either sequentially or in parallel. At least one transfer pin in the array may be independently positionable for alignment with respect to the opening of a target storage receptacle. Individual transfer pins in the array also may be free floating or spring loaded.

In such a system, the dispensed sample may be from 0.2 to 100 nanoliters. The transfer pin may have a diameter greater than the opening of the target storage receptacle. The sample liquid may be a polar liquid such as aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solutions.

An embodiment may further include a voltage controller that applies a high voltage potential, for example, 100V to 5kV, between the pin tip and the target receptacle to aid the capillary action. The voltage controller may apply the high voltage potential before or after the transfer pin is positioned at the target storage receptacle, and removes the high

voltage potential after the transfer pin is moved away from the target storage receptacle. The voltage controller also may use a resistor network and/or a controllable switch in series with the transfer pin.

In a system, the storage device may use evaporation control measures to control evaporation of dispensed samples from the storage receptacles. This may include immersing the storage receptacles in an immiscible liquid such as a perfluorinated hydrocarbon and/or at least one of humidity control, fluid pressure, and receptacle cooling.

The positioning module may position the dispenser so that the at least one transfer pin makes direct contact with target storage receptacle for transferring the sample liquid, or so that the at least one transfer pin is near the target storage receptacle without direct contact for transferring the sample liquid.

The liquid dispenser may operate to sequentially transfer multiple samples to the target storage receptacle to produce a layered sample pattern. The at least one transfer pin may be able to dispense multiple samples without replenishment.

The capillary action may be aided by vibrating the transfer pin or the target receptacle. The pin tip may have a slotted end, for example, and X-shaped slotted end. The pin tip may have one or more structural features that increase the surface area of the sample liquid at the pin tip. These structural features may include one or more features from the group of slots, grooves, and spirals. The target receptacle may be substantially empty prior to transferring the sample liquid.

Brief Description of the Drawings

The present invention will be more readily understood by reference to the following detailed description taken with the accompanying drawings, in which:

Figure 1 shows a cut away view of a nanotiter plate having one of its through wells being loaded by a transfer pin bearing a liquid sample according to one embodiment of the present invention.

Figure 2 shows an elevated side view of an array of transfer pins according to one embodiment of the present invention.

Detailed Description of Specific Embodiments

Various embodiments of the present invention are directed to using capillary action

to transfer a microfluidic volume of a liquid sample from a transfer pin to a suitable target receptacle. The target storage receptacle typically will have an affinity for the sample liquid, and could be a flat surface; a surface with indentations, close ended wells, or pores; a membrane or filter; a gel; or a platen with close-ended wells or through-hole wells. In one specific embodiment, the target receptacle is one or more wells in an array of through-hole wells as part of a parallel and/or series sample transfer process. In other embodiments, the target storage receptacle may be a hydrophilic spot or divot in a hydrophobic background. Such an environment may be established on a coated glass slide such as the ones available from Erie Scientific of Portsmouth, NH.

Figure 1 shows a cut away view of a nanotiter plate having one of its through-hole wells being loaded by a transfer pin bearing a liquid sample according to one embodiment of the present invention. Platen **10** contains a large number of through-hole wells **12** that traverse the platen **10** from one planar surface **14** to the other opposing planar surface (not shown). The platen **10** is may be from 0.1 mm to more than 10 mm thick; for example, around 0.3 to 1.52 mm thick, and commonly 0.5 mm. The thickness of platen **10** is also the length of the through-hole wells **12** when they are oriented perpendicularly to planar surface **14**. The length and volume of the wells **12** can be increased somewhat by orienting them at an angle to surface **14**. The wells **12** are the target receptacles for the liquid samples from the transfer pin.

Typical microfluidic volumes of the through-hole wells **12** could be from 0.1 picoliter to 1 microliter, with common volumes in the range of 0.2-100 nanoliters. Capillary action or surface tension of the sample liquid may be used to load the wells **12**. To enhance the drawing power of the wells **12**, the target area of the receptacle, interior walls **42**, may have a hydrophilic surface that attracts the sample liquid. Alternatively, the wells **12** may contain a porous hydrophilic material that attracts the sample liquid. To prevent cross-contamination (crosstalk), the exterior planar surfaces **14** of platen **10** and a layer of material **40** around the openings of wells **12** may be of a hydrophobic material. Thus, each well **12** has an interior hydrophilic region bounded at either end by a hydrophobic region.

In some systems, the well **12** may be submersed in an immiscible, non-conducting liquid such as perfluorinated hydrocarbon, hydrocarbon, or silicone fluid. An immiscible liquid prevents evaporation of the sample liquid from the wells **12** and further protects the

dispensed samples from cross-communication. Of course, other evaporative control measures may also be useful, including without limitation, humidity control, fluid pressure, platen cooling, etc.

Transfer pin **20** is generally dowel-shaped, made of stainless steel, titanium, or other durable material, with a flat, rounded, tapered, or cupped tip. Typically, although not necessarily, the diameter of the transfer pin **20** is greater than the diameter of the wells **12** in order to have more rigidity in the pin and to allow the pin to reliably contact the side walls of the well to facilitate docking between the pin and the well that would otherwise require much more precise positioning measures.

Transfer pin **20** may also have slots, grooves or spirals cut into it to increase volumetric capacity and/or to better meter the dispensing action. The slots, grooves, or spirals also increase the surface area of the sample liquid available for contact with hydrophilic receptacle walls. Transfer pin **20** may be capable of holding and/or delivering anywhere from 0.1 picoliters to more than 10 microliters, but typically holds 0.1 nanoliters to 4 microliters.

Figure 1 shows an embodiment of the transfer pin **20** having a tapered tip with a tapered slot that holds the sample liquid. In such an embodiment, the tapered end is small enough to fit inside the well **12**, but the overall pin diameter is still larger than the diameter of the well. In the embodiment shown, the tapered end of the transfer pin **20** forms a 40 degree angle, and the tapered slot within this end forms a 14 degree angle. This transfer pin **20** holds adequate amounts of sample liquid (~0.5 μl), facilitates wicking of the sample liquid to the tip of the pin, and can fill multiple wells **12** in succession without replenishment. The slotted end may use two approximately perpendicular slots forming an X-shape. In an alternative embodiment, the transfer pin **20** is a simple stainless steel dowel with one or more slots in the end. In another embodiment, the transfer pin **20** is a simple stainless steel dowel with a rounded tip and one or more slots in the end.

Transfer pin **20** may be free to move perpendicular to the surface **14** of the platen **10**, but movement may be constrained in a plane parallel to the surface; this implementation is referred to as a floating pin. However, alternative embodiments of the invention may also be implemented with fixed transfer pins **20** as well. It is generally desirable to achieve good contact between the transfer pin **20** and the target area, but not to damage the target receptacle, well **12**. This objective may be achieved by using a floating model transfer pin

20. Floating gravity-fed or spring-loaded transfer pins **20** help with reliable positioning of multiple pins to properly contact corresponding wells **12** to overcome minor errors in alignment. In some embodiments, spring-loaded transfer pins **20** may be used, preferably with "soft" springs having a spring constant that allows for relatively large displacement with a small applied force. In other embodiments, gravity-fed floating transfer pins **20** may be more advantageous in applying minimum force to a target well **12**. However, gravity-fed transfer pins **20** may occasionally stick in one position following a sample dispensing cycle. One solution to this problem is to use a pressure or vacuum manifold to assist with pin positioning, such as a vacuum manifold that sucks the transfer pin **20** back into position between dispensing cycles. Floating transfer pins **20** may also use magnetism or electro-magnetism for pin positioning, such as use of a strong magnetic field for uniformly extending pins, use of magnetic pins, or by accelerating and rapidly decelerating individual pins or the entire array.

Typically, transfer pin **20** is loaded with sample liquid for transfer to platen **10**. In typical embodiments, the sample liquid may be an aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solution. Then, transfer pin **20** is moved to a position over the well **12** to be loaded. The transfer pin **20** is lowered until contact is made with the opening of the well **12**. When the tip of transfer pin **20** is tapered, as shown in Fig. 1, there is maximal contact between the outer surface of the pin and the surface of the interior walls **42** of well **12**. Such maximal contact between pin tip and well wall is desirable because the sample liquid held in the transfer pin **20** needs to contact the interior wall **42** of the well **12** in order for transfer from the pin to be initiated. Furthermore, a tapered pin tip can correct for slight errors in pin placement with respect to the wells, as the taper of the transfer pin **20** guides it into the exact desired position.

Proper positioning of the transfer pin **20** (or arrays of transfer pins) relative to the well **12** (or array of wells) is important for making contact sufficient to effect transfer the sample liquid from the transfer pin **20** to the well **12**. This may be accomplished, for example, by use of precisely machined guide plates that holds the transfer pin **20** (or an array of pins) in proper position via at least one hole in the guide plate. In one embodiment, the guide plate holes are slightly larger in diameter than the transfer pins to allow the pins to slide into the optimal position as they are brought into contact with the wells **12**. In another embodiment, two guide plates may be used to position the transfer pin

20, a lower guide plate having a smaller diameter guide hole than the upper guide plate. A transfer pin **20** may have a shoulder on it that restricts its downward travel, but which allows the transfer pin **20** to move upward in response to a force such as produced when the pin docks with the well **12**. Fine positioning of the transfer pin **20** and well **12** may be aided by vibrating either.

Once the transfer pin **20** is positioned in contact with the opening of well **12**, a portion of the sample liquid in the pin will be wicked by capillary action into the well **12** (and displace any immiscible liquid which may previously have been stored therein). The volume of sample liquid that is transferred is self-metered by the volume of the well **12**, and subject to other environmental variables, such as the action of the layers of hydrophilic and hydrophobic materials, whether the target area is under an immiscible fluid, and if so, the height of the immiscible fluid over the target area, the duration of contact with the area, the speed of withdrawal from the area, and various of the other variables listed above with respect to pin transfer. In the prior art, transfer of sample liquid has been into wells such as in a 384-well plate that are usually pre-filled with a liquid and the pins have been substantially smaller than the receptacle wells. In some embodiments of present invention, the well **12** may be substantially empty before transferring the sample liquid into it.

Initializing the wicking action and wetting the interior walls **42** of the well **12** is an important point in the transfer process. Some embodiments will have little difficulty establishing good contact between the sample liquid held by the transfer pin **20** and the interior walls **42** of the well **12** sufficient to cause self-metered transfer of the sample liquid to the well **12**. Several factors affect the ability for this action to happen, among which are that the interior walls **42** must be sufficiently hydrophilic, and the use of one or more slots in the pin tip of the transfer pin **20** to maximize the exposed surface area of the sample liquid. Preferably the slots will have a reservoir cavity as well as geometry that minimizes the coefficients of variance of loading (related to the standard deviation of volume dispensed in multiple loading cycles) by causing the amount transferred to be a small fraction of the total volume held by the slot reservoir. A slot reservoir in the transfer pin **20** also provides the option of multiple sample transfers from the pin from a single load of sample from a source microplate.

Occasionally, for a variety of reasons, not all of which are well understood, there

will be difficulty establishing this wicking flow. Some embodiments overcome such difficulties in initiating the transfer of sample liquid to a storage receptacle by applying a high voltage electric potential. Although this approach may be useful for non-polar sample liquids, it is especially useful for transferring polar sample liquids such as aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solutions can be transferred into a target well **12** by contacting a transfer pin **20** filled with sample liquid and applying a high voltage with low current (typically less than 5 microamps). Initiation of capillary action may also be aided by vibrating the transfer pin **20** or the target well **12**.

Embodiments of the present invention use the existing transfer pin and platen well arrangement described with respect to Fig. 1 above, and add a high voltage potential to the transfer pin **20**, or at least the tip of the pin. Such an arrangement differs from that described in the '815 patent in that it avoids the need for a complex plate insulation arrangement (as shown in its Fig. 1), and it does not use the electrokinetic relationship of voltage-time to volume transferred. In embodiments where transfer pin **20** is in direct contact with the receptacle target area, the electric charge applied to transfer pin **20** is not directly related to the duration of the sample liquid transfer or the amount dispensed. That purpose is accomplished by hydrophilic attraction of the interior walls **42** and the self-metering action of the platen wells **12**. Rather the electrical charge on the transfer pin **20** serves as an activation energy that excites the sample liquid held by the pin to encourage the wetting of a liquid bridge flow channel between the transfer pin **20** and the interior walls **42** of well **12**. The amount of sample liquid that is dispensed in a specific embodiment is dependent upon a multitude of variables such as pin geometry, pin coating, sample liquid surface tension, wetted depth, speed of transfer, sample liquid viscosity, sample liquid conductivity, the concentration of particles in the sample liquid, voltage level, voltage duration, voltage frequency, and loading environment (*e.g.*, air vs. under liquid). Careful control of these variables is required. In some embodiments, it may be useful to apply the voltage to the well **12** rather than to the transfer pin **20**.

The voltage necessary to effect transfer of the sample liquid depends on the physical properties of the sample liquid and the receptacle, *i.e.*, well **12**, including their affinity for each other. In addition, the choice between AC and DC voltage supplies may affect the voltage necessary for transfer of the sample liquid, but both types of supplies are acceptable. Generally, the voltage will be between 10V and 50 kV, typically in the range

of 100V to 5 kV. The choice of voltage level is affected by effects of ohmic-related heating and material breakdown characteristics. With a high dielectric constant liquid, a high voltage of large voltage pulse may be applied without electrical breakdown.

It is desirable to limit the current flowing from the transfer pin **20** in order to prevent electrical heating, etching and ionization of the sample liquid, receptacle, pins, air, or immiscible fluid. Therefore, it is important to use a high-voltage, low current system. Examples high-voltage, low current sources include a Van De Graaf generator, or a standard high voltage source in series with a high-voltage, high-resistance resistor.

In one specific embodiment, the voltage is applied to the transfer pin **20** after it is positioned at the opening of the desired well **12**, and the voltage is removed after the sample liquid has been transferred to the well **12** and the transfer pin **20** has been withdrawn from the opening of the well **12**. In other embodiments, the voltage may be applied to the transfer pin **20** before it is positioned at the opening of the desired well **12**, and the voltage is removed after the sample has been transferred to the well **12** but before the transfer pin **20** has been withdrawn from the opening of the well **12**.

In addition, voltage aided transfer of sample liquid in various embodiments may be based on either full, partial, or no physical contact between the transfer pin **20** and the target well **12**. That is, in some embodiments, the end of the transfer pin **20** may be brought into substantial physical contact with a portion of the target well **12** in order to transfer the sample liquid from the pin to the well. In other embodiments, the transfer pin **20** approaches the opening of the target well **12** without actually establishing significant contact in order to transfer the sample liquid from the pin to the well. Some embodiments with or without contact may benefit from electrospray effect to transfer the sample liquid from the transfer pin **20** to the target well **12**.

In various embodiments, either the target well **12** or the entire platen **10** may be electrically grounded. In other embodiments, the platen **10** and well **12** may be ungrounded. Either approach may be successful so long as there is an appropriate voltage difference between the transfer pin **20** and the target well **12**. In addition, the platen **10,** itself, may be made of conductive material, or non-conductive material. Moreover, specific embodiments may not necessarily require a combination of hydrophilic and hydrophobic materials as described with respect to Fig. 1, but may be able to exploit the invention using receptacle structures without any significant hydrophobic or hydrophilic

characteristics, or in ones with all hydrophobic or all hydrophilic materials.

The efficiency of voltage aided transfer of the sample liquid also may depend on the relative geometries of the transfer pin **20** and the target well **12**. For example, a transfer pin **20** with a tapered point such as shown in Fig. 1, may be more effective than a different shaped end such as a flat one. In one specific embodiment in which the well **12** is 280 microns in diameter, a pointed pin tip of less than 200 microns, *e.g.*, 140 microns, may be most effective. In some specific embodiments, a blunt pin tip also may work, but in other embodiments, such as under dense fluids, a blunt pin tip without a sufficient point on its end may not be operable in a voltage aided transfer arrangement since the sample liquid may climb the sides of the transfer pin **20**.

In addition to use of an individual transfer pin **20** as shown in Fig. 1, an embodiment may be based on a multiple pin array **30**, such as the one shown in Figure 2, which is designed so that each transfer pin **20** is spaced to address a unique well **12** in the platen **10**. In Fig. 2, multiple transfer pins **20** are held in an array by an electrical insulating plate **32**. The bottoms of the transfer pins **20** may be slotted as shown in Fig. 2, or have some other geometry for holding the sample liquid for dispensing. In addition, the bottoms of the transfer pins **20** may be squared off as shown in Fig. 2, or may be tapered as in Fig. 1, or have some other shape geometry.

The top side of each of the transfer pins **20** may be electrically connected either directly or via a resistor, switch, or transistor to a voltage source. The voltage may be specific for each transfer pin **20**, or multiple transfer pins **20** may share a common voltage source.

The top sides of the transfer pins **20** are electrically connected to pin voltage sources **36** in a voltage control array **34**, which may optionally include a voltage control port **38** addressable by an external processor. Each individual pin voltage source **36** may be, for example, a resistor element in a resistor network (*i.e.*, the voltage control array **34**) connected to a high voltage source so that each transfer pin **20** is connected via its own resistor to the high voltage source. To reduce the cost and size of the system, a single source resistor may be placed between the high voltage source and the resistor network, which allows the use of smaller, cheaper lower resistance resistors in the network together with a single bulky, more expensive, high-resistance resistor at the source. For example, the source resistor could be a 1 to 10 gigohm resistor, and the pin resistors could be 1 to 10

megohms each. However, it may be advantageous in terms of uniformity of transfer throughout the pin array **30** to have a higher resistance on the pin resistors, for example each pin having a gigohm resistor.

To individually actuate at least one transfer pin **20** using voltage application, a controllable switch may be placed in series with each actuable pin. These switches may be, for example, high voltage transistors or relays, and also may be controlled by a microprocessor. In one specific embodiment, each spring-loaded transfer pin **20** may be loaded on a spring, which also acts as an electrical contact to a printed circuit board voltage control array **34**. The printed circuit board voltage control array **34** may contain the resistor network and connections to the high voltage source. In some embodiments, the printed circuit board voltage control array **34** also may contain the switch networks and connections to the computer or other device for selecting a sample dispensing pattern.

Thus, in one embodiment, each transfer pin **20** in a multiple pin array **30** is individually addressable for purposes of applying a high voltage potential to the pin. In such a pin array **30**, one transfer pin **20** at a time may be actuable, multiple pins may be actuable at one time, or all of the pins in the array may be actuable at one time. The more transfer pins **20** that are actuated at any one time, the greater the parallel processing of the system. By actuating different patterns of multiple transfer pins **20** (in a manner analogous to an ink jet computer printer) patterns of dispensed samples may be developed. By repeating this process, layered sample patterns may be developed, including the synthesis of organic molecules such as peptides, small molecules or oligonucleotides.

In another embodiment, a pin array may be equipped with a controller for selectively extending or retracting a subset of transfer pins **20** to cause contact or removal from contact of those pins for the purpose of dispensing a pattern of sample. For example, an array of solenoids could be used to retract those transfer pins **20** that are not desired to contact the receptacle well **12**. The solenoids may act directly on the transfer pin **20**, or by a remote drive mechanism such as an array of pistons positioned slidably in an array of tubes. Alternatively, an array of controllable valves connected to a vacuum or pressure manifold may be used to selectively retract or extend a subset of transfer pins **20**. Moving the pins in the array **30** so that only transfer pins **20** selected for sample transfer approach the opening of selected wells **12** avoids inadvertent transfer of the sample liquid from non-selected pins to non-selected wells, such as by wetting, which may occur even when no

voltage is applied to a non-selected pin. It may be desirable to both selectively actuate a pattern of transfer pins **20** using both movement controllers and application of high voltage to the selected pins in order to prevent inadvertent dispensing, such as by electrospray.

Although various exemplary embodiments of the invention have been disclosed, it should be apparent to those skilled in the art that various changes and modifications can be made which will achieve some of the advantages of the invention without departing from the true scope of the invention.

What is claimed is:

1. A microfluidic liquid dispenser for an assay system, the dispenser comprising:
at least one transfer pin for transferring a microfluidic sample of liquid to a target receptacle; and
a pin tip at one end of the transfer pin structured to cooperate with an opening in the target receptacle for using capillary action to transfer the sample from the at least one transfer pin to the target receptacle.

2. A liquid dispenser according to claim 1, wherein the target receptacle is a through-hole well in a platen array of wells.

3. A liquid dispenser according to claim 1, wherein the target receptacle is a closed-ended well in a platen array of wells.

4. A liquid dispenser according to claim 1, wherein the target receptacle includes hydrophilic walls regions that attract the sample.

5. A liquid dispenser according to claim 1, wherein the target receptacle includes an opening having a hydrophilic region surrounded by hydrophobic material.

6. A liquid dispenser according to claim 1, further comprising:
a transfer pin array including a plurality of transfer pins for transferring a plurality of samples to a corresponding plurality of target receptacles.

7. A liquid dispenser according to claim 6, wherein individual transfer pins in the array are sequentially actuable.

8. A liquid dispenser according to claim 6, wherein at least one transfer pin in the array is independently positionable for alignment with respect to the opening of a target receptacle.

9. A liquid dispenser according to claim 6, wherein at least one individual transfer pin in the array is gravity-fed floating.

10. A liquid dispenser according to claim 1, wherein the microfluidic sample is from 0.2 to 100 nanoliters.

11. A liquid dispenser according to claim 1, wherein the transfer pin has a diameter greater than the opening of the target receptacle.

12. A liquid dispenser according to claim 1, wherein the sample is a polar liquid.

13. A liquid dispenser according to claim 12, wherein the polar liquid is an aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solution.

14. A liquid dispenser according to claim 1, wherein a high voltage potential is applied to at least one of the pin tip and the target receptacle to aid the capillary action.

15. A liquid dispenser according to claim 14, wherein the high voltage potential is between 100V and 5kV.

16. A liquid dispenser according to claim 14, further comprising:

a voltage control module for controlling when the high voltage potential is applied to and removed.

17. A liquid dispenser according to claim 16, wherein the voltage control module operates to apply the high voltage potential before the transfer pin is positioned at the target receptacle, and to remove the high voltage potential after the transfer pin is moved away from the target receptacle.

18. A liquid dispenser according to claim 16, wherein the voltage control module includes a resistor network.

19. A liquid dispenser according to claim 16, wherein the voltage control module includes a controllable switch in series with the transfer pin.

20. A liquid dispenser according to claim 1, wherein the capillary action is aided by vibrating at least one of the transfer pin and the target receptacle.

21. A liquid dispenser according to claim 1, wherein the at least one transfer pin is able to dispense multiple samples without replenishment.

22. A liquid dispenser according to claim 1, wherein the pin tip has a slotted end.

23. A liquid dispenser according to claim 21, wherein the slot is X-shaped.

24. A liquid dispenser according to claim 1, wherein the pin tip has one or more structural features that increase the surface area of a sample at the pin tip.

25. A liquid dispenser according to claim 24, wherein the structural features include one or more features from the group of slots, grooves, and spirals.

26. A liquid dispenser according to claim 1, wherein the target receptacle is substantially empty prior to transferring the sample.

27. A method for use in dispensing a microfluidic sample of a liquid, the method comprising:

providing at least one transfer pin for transferring a microfluidic sample of liquid to a target receptacle, one end of the transfer pin having a pin tip structured to cooperate with an opening in the target receptacle; and

using capillary action between the pin tip and the target receptacle to transfer the sample from the at least one transfer pin to the target receptacle.

28. A method according to claim 27, wherein the target receptacle is a through-hole well in a platen array of wells.

29. A method according to claim 27, wherein the target receptacle is a closed-ended well in a platen array of wells.

30. A method according to claim 27, wherein a high voltage potential is applied to at least one of the transfer pin and the target receptacle to aid the capillary action.

31. A method according to claim 30, wherein the high voltage potential is between 100V and 5kV.

32. A method according to claim 30, further comprising:
controlling when the high voltage potential is applied and removed.

33. A method according to claim 32, wherein the controlling step includes applying the high voltage potential before the transfer pin is positioned at the target receptacle, and removing the high voltage potential after the transfer pin is moved away from the target receptacle.

34. A method according to claim 32, wherein the controlling step uses a resistor network.

35. A method according to claim 32, wherein the controlling step uses a controllable switch in series with the transfer pin.

36. A method according to claim 27, wherein the target receptacle includes hydrophilic walls that attract the sample.

37. A method according to claim 27, wherein the target receptacle includes an opening surrounded by hydrophobic material.

38. A method according to claim 27, further comprising:
providing a transfer pin array including a plurality of transfer pins for transferring a plurality of samples to a corresponding plurality of target receptacles.

39. A method according to claim 38, wherein individual transfer pins in the array are sequentially actuable.

40. A method according to claim 38, wherein at least one transfer pin in the array is independently positionable for alignment with respect to the opening of a target receptacle.

41. A method according to claim 38, wherein at least one transfer pin in the array is gravity-fed floating.

42. A method according to claim 27, wherein the microfluidic sample is from 0.2 to 100 nanoliters.

43. A method according to claim 27, wherein the transfer pin has a diameter greater than the opening of the target receptacle.

44. A method according to claim 27, wherein the sample is a polar liquid.

45. A method according to claim 44, wherein the polar liquid is an aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solution.

46. A method according to claim 27, further comprising:
applying evaporation control measures to the target receptacle.

47. A method according to claim 46, wherein the applying step includes immersing the target receptacle in an immiscible liquid.

48. A method according to claim 47, wherein the immiscible liquid is a perfluorinated hydrocarbon, hydrocarbon, or silicone fluid.

49. A method according to claim 46, wherein the applying step uses at least one of humidity control, fluid pressure, and receptacle cooling.

50. A method according to claim 46, wherein the applying step includes positioning the transfer pin in direct contact with target receptacle.

51. A method according to claim 46, wherein the applying step includes positioning the transfer pin near the target receptacle without direct contact.

52. A method according to claim 27, further comprising:
sequentially transferring multiple samples to the target receptacle to produce a layered pattern of samples.

53. A method according to claim 27, wherein the at least one transfer pin is able to dispense multiple samples without replenishment.

54. A method according to claim 27, wherein the capillary action is aided by vibrating at least one of the transfer pin and the target receptacle.

55. A method according to claim 27, wherein the pin tip has a slotted end.

56. A method according to claim 56, wherein the slotted end is X-shaped.

57. A method according to claim 27, wherein the pin tip has one or more structural features that increase the surface area of a sample at the pin tip.

58. A method according to claim 57, wherein the structural features include one or more features from the group of slots, grooves, and spirals.

59. A method according to claim 27, wherein the target receptacle is substantially empty prior to transferring the sample.

60. A microfluidic assay system comprising:
at least one liquid sample storage device including a plurality of storage receptacles; and
a microfluidic liquid dispenser having at least one transfer pin for using capillary action to transfer a microfluidic sample of liquid to a target storage receptacle, one end of the transfer pin having a pin tip structured to cooperate with an

opening in the target storage receptacle; and

a dispenser positioning module that positions the liquid dispenser to enable the transfer pin to cooperate with the target receptacle for transferring the sample.

61. An assay system according to claim 60, wherein the storage device is a platen array of through-hole wells.

62. An assay system according to claim 60, wherein the storage device is a platen array of closed-ended wells.

63. An assay system according to claim 60, wherein the target storage receptacle includes hydrophilic walls that attract the sample.

64. An assay system according to claim 60, wherein the target storage receptacle includes an opening surrounded by hydrophobic material.

65. An assay system according to claim 60, wherein the liquid dispenser includes a transfer pin array including a plurality of transfer pins for transferring a plurality of samples to a corresponding plurality of target storage receptacles.

66. An assay system according to claim 60, wherein individual transfer pins in the array are sequentially actuable.

67. An assay system according to claim 60, wherein at least one transfer pin in the array is independently positionable for alignment with respect to the opening of a target storage receptacle.

68. An assay system according to claim 60, wherein at least one transfer pin in the array is gravity-fed floating.

69. An assay system according to claim 60, wherein the microfluidic sample is from 0.2 to 100 nanoliters.

70. An assay system according to claim 60, wherein the transfer pin has a diameter greater than the opening of the target storage receptacle.

71. An assay system according to claim 60, wherein the sample is a polar liquid.

72. An assay system according to claim 71, wherein the polar liquid is an aqueous, DMSO, dimethylformamide (DMF), or acetonitrile solution.

73. An assay system according to claim 60, wherein a voltage controller applies a high voltage potential between the pin tip and the target storage receptacle to aid the capillary action.

74. An assay system according to claim 73, wherein the high voltage potential is between 100V and 5kV.

75. An assay system according to claim 73, wherein the voltage controller applies the high voltage potential before the transfer pin is positioned at the target storage receptacle, and removes the high voltage potential after the transfer pin is moved away from the target storage receptacle.

76. An assay system according to claim 73, wherein the voltage controller uses a resistor network.

77. An assay system according to claim 73, wherein the voltage controller uses a controllable switch in series with the transfer pin.

78. An assay system according to claim 60, wherein the storage device uses evaporation control measures to control evaporation of samples from the storage receptacles.

79. An assay system according to claim 78, wherein the evaporation control measures include immersing the storage receptacles in an immiscible liquid.

80. An assay system according to claim 79, wherein the immiscible liquid is a perfluorinated hydrocarbon, hydrocarbon, or silicone fluid.

81. An assay system according to claim 78, wherein the evaporation control measures include at least one of humidity control, fluid pressure, and receptacle cooling.

82. An assay system according to claim 60, wherein the positioning module positions the dispenser so that the at least one transfer pin makes direct contact with target storage receptacle for transferring the sample.

83. An assay system according to claim 60, wherein the positioning module positions the dispenser so that the at least one transfer pin is near the target storage receptacle without direct contact for transferring the sample.

84. An assay system according to claim 60, wherein the liquid dispenser operates to sequentially transfer multiple samples to the target storage receptacle to produce a layered pattern of samples.

85. An assay system according to claim 60, wherein the at least one transfer pin is able to dispense multiple samples without replenishment.

86. An assay system according to claim 60, wherein the capillary action is aided by vibrating at least one of the transfer pin and the target receptacle.

87. An assay system according to claim 60, wherein the pin tip has a slotted end.

88. An assay system according to claim 87, wherein the slotted end is X-shaped.

89. An assay system according to claim 87, wherein the pin tip has one or more structural features that increase the surface area of a sample at the pin tip.

90. An assay system according to claim 89, wherein the structural features include one or

more features from the group of slots, grooves, and spirals.

91. An assay system according to claim 60, wherein the target receptacle is substantially empty prior to transferring the sample.

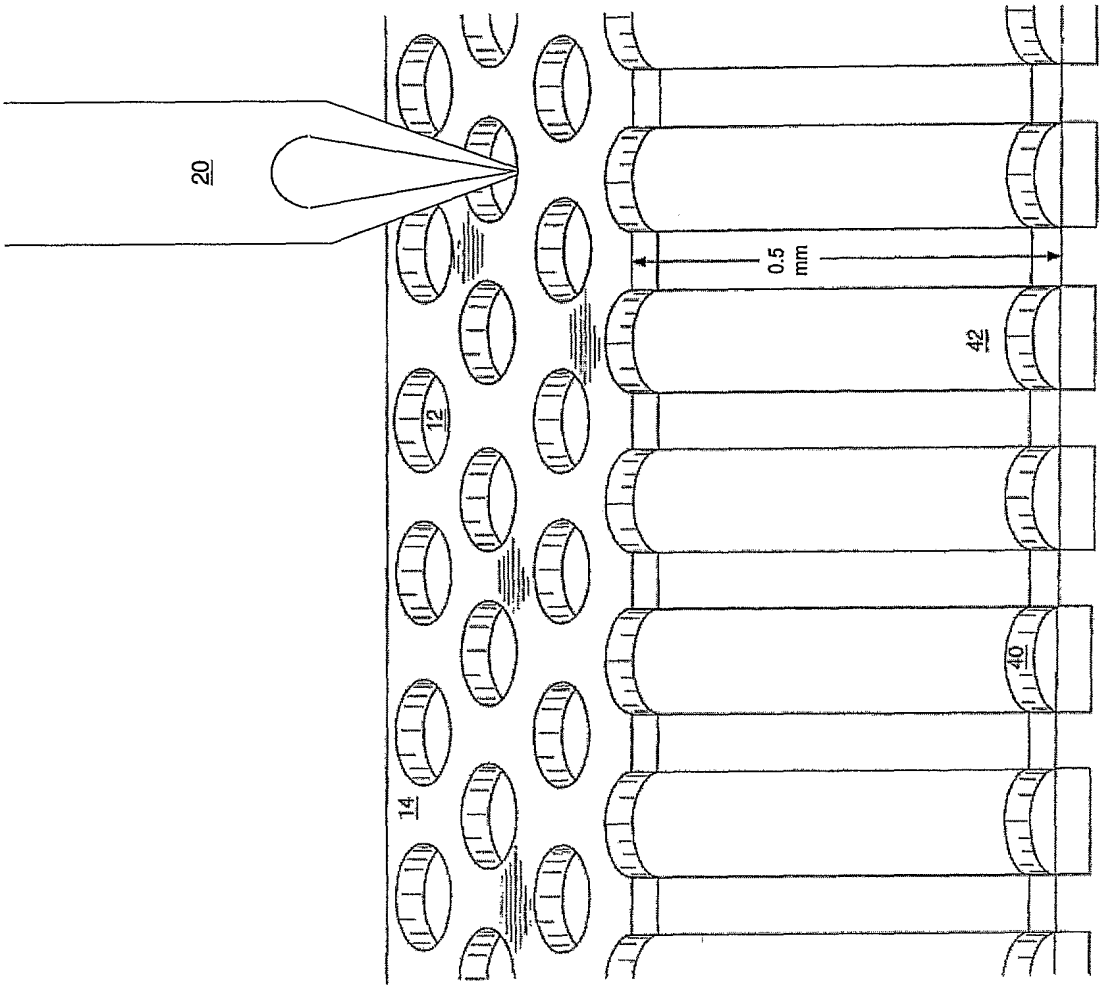

Figure 1

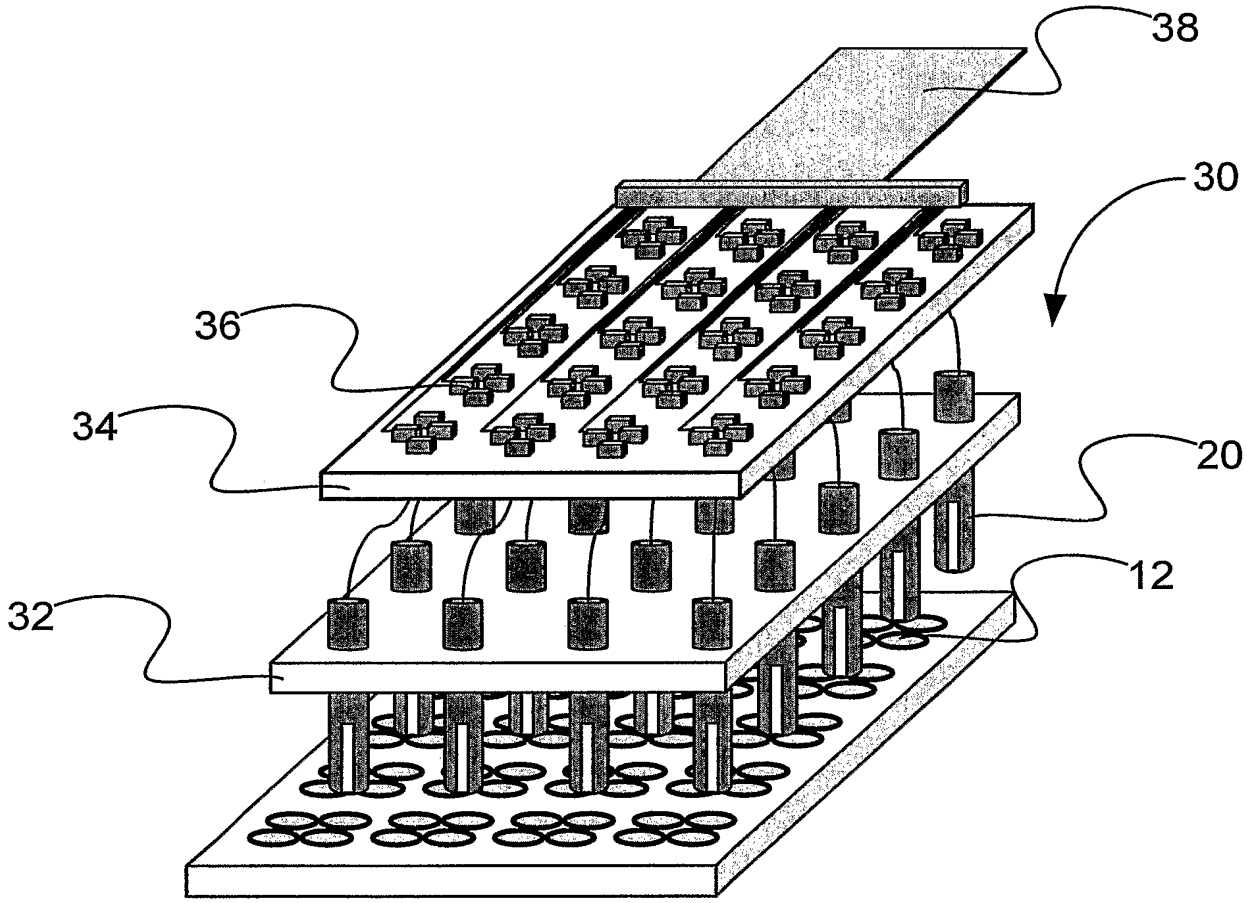

Figure 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/26441

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2003	02/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wyplosz, N

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